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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/579,357

Filing Date: May 16, 2006

Appellant(s): BOLLI ET AL.

Elizabeth A. Doherty
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/3/11 appealing from the Office action mailed 6/7/11.

(1) Real Party in Interest

A statement identifying by name and the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

Claims 29-45 are subject to this appeal.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after the office action mailed on 6/7/11 contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The claimed subject matter relates to a stable polyclonal IgG preparation. Appellant is deemed to relate the claimed polyclonal IgG as the therapeutic immune globulins prepared from pools of human plasma. However, the art recognizes that the polyclonal IgG is raised from any animals by multiple injections of the relevant antigen and an adjuvant ('586 patent, of record, col. 11, under polyclonal antibody).

Appellant relies on Tankersley, Lemm and Cramer references (note Exhibits) for characteristics and stability issues of human polyclonal IgG associated with ethanol precipitation during the purification of human polyclonal IgG pooled from human plasma (Brief, p. 8-11). The specification does not disclose that the polyclonal IgG is limited to human polyclonal IgG that is suitable for intravenous administration as disclosed by the Tankersley, Lemm and Cramer references. The claimed subject matter is contemplated broader than the human polyclonal IgG prepared from the pool of human plasma.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the ground of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

U. S. Pat. No. 6,171,586	Lam et al.	01-2001
U. S. Pub. No. 2005/0142139A1	Schulke et al.	01-2005

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,171,586 (IDS reference filed on 5/16/06, of record) in view of U.S. Pub. 2005/0142139A1 (of record).

The '586 patent teaches a stable aqueous pharmaceutical formulation comprising a buffer at about pH 4.8 and the antibody encompasses polyclonal antibody (col. 7-8, claims 1-29). Note that the '586 patent includes polyclonal antibody in the antibody (col. 7).

Given that the '586 patent does not disclose nicotinamide, the claimed limitation "wherein the preparation does not comprise nicotinamide" has been met.

The disclosure of the '586 patent differs from the claimed invention in that it does not teach the use of proline as is currently recited in claim 29 of the instant application.

The '139 publication teaches CD4-IgG2 antibody formulation comprising a histidine buffer and proline at about pH 5.5 (claims 29-39, [0032]). Given that the specification on p.4 of the instant application discloses that all naturally occurring amino acid is L-amino acid and the '139 publication discloses naturally occurring amino acids, it meets the limitations of claims 33-36 of the instant application.

As the '139 publication does not disclose any use of nicotinamide as a stabilizer, the referenced formulation is considered to be made in the absence of nicotinamide. Thus, it meets the claimed limitation of claim 29.

Further, the '139 publication teaches that the concentration of the antibody is 15-162mg/ml ([0045-47]) and proline concentration of "about" 25-150mM ([0013]).

Note the term "about" is flexible and includes unrecited limitations near the recited limitation. Given that the '139 publication teaches the proline concentration of "about" 150mM and reads on claimed limitation of "0.2M", claims 33, 35-39 and 42-45 are included in this rejection.

As is evidenced by the specification on p. 6 of the instant application, 10% of IgG is equivalent to 100g/L. Given that the concentration of 100g/L is equivalent to 100mg/ml, the referenced about 100-162mg/ml that are suitable for subcutaneous or IV are equivalent to 10-16.2% (w/v) ([0007, 0049]) and claims 30-45 are included in this rejection.

Further, claims 34, 36 and 40 reciting "wherein the preparation is a liquid preparation that has not been lyophilized and is not lyophilized prior to administration" are included in this rejection because the '139 publication specifically recites "stable following at least one freeze and thawing of formulation" (claim 16) which differentiate the physical condition of the formulation from recited "lyophilized" (claim 15) which is subject to lyophilization. The prior art "freeze thawing" does not constitute "drying" that is required for "lyophilization". Also, the formulation of the '139 publication in claims 1 and 22-23 recites that the prior art formulation is a liquid formulation (e.g. administered intravenously) and it is differentiated from the lyophilized formulation (e.g. claim 15) and thus reads on the claimed limitation of "wherein the preparation is a liquid preparation that has not been lyophilized and is not lyophilized prior to administration".

Therefore, the reference teaches the claimed limitation.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to add proline as a stabilizer as taught by the '139 publication to the antibody formulation as taught by the '586 patent.

Therefore, it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the addition of proline improves stability of protein upon storage and delivery by reducing aggregation.

From the teachings of the references, it would have been obvious to one of ordinary skill in the art to combine teachings of the references and there would have been a reasonable expectation to success in producing the claimed invention. Therefore, the invention as a whole was a prima facie obvious to one of ordinary skill in the art at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Appellant's arguments filed on 10/3/11 have been fully considered but they were not persuasive.

At pages 16-20 of the Brief, Appellant has argued that the '586 patent and the '139 publication do not relate to polyclonal IgG preparations. Further, Appellant has asserted that there is no motivation to add proline and there is no reasonable expectation of success to result in the claimed invention (Brief, p. 21-22). Further, Appellant has asserted that the proline pH range is not taught by any cited prior art (Brief, p. 21-24) or single out proline as a possible stabilizer.

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At pages 24-30 of the Brief, Appellant has asserted that the claimed invention shows unexpected results and commercial success and HIZENTRA® and PRIVIGEN® have been submitted to support this assertion.

At pages 22-55 of the Brief, Applicant has provided essentially identical arguments for claims 30-44 of the instant application as claim 29 at pages 9-21 of the Brief, no separate response will be provided for such claims herein.

Contrary to Appellant's arguments, the antibody formulations taught by the '586 patent encompass the claimed "polyclonal IgG preparation". Antibody is defined as any various proteins in the blood that are generated in the reaction to foreign proteins or polysaccharides neutralize them and so produce immunity while immunoglobulin is defined as a group of blood serum protein that acts as antibody. Therefore, art recognizes immunoglobulin as antibody and uses immunoglobulin and antibody interchangeably. There are various immunoglobulin isotypes that classify IgG, IgA, IgD, IgE and IgM based on the structural differences and their multimeric nature (IgA is a dimer, IgM is a pentamer) and IgG is most abundant in the blood serum, the immunoglobulin (e.g. antibody) is contemplated as IgG unless other isotype of antibody is designated (Tankersley reference, see exhibit, p. 160 of the reference, Lemm reference, see exhibit, p. s28-s31). Additionally, the '586 patent states the following:

The term antibody is used in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies) and antibody fragments so long as they exhibit the desired biological activity (col. 7, lines 52-58).

Therefore, contrary to Appellant's assertion in that the '586 patent does not relate to polyclonal IgG, the antibody (e.g. immunoglobulin) disclosed in the '586 patent encompasses the polyclonal IgG.

Appellant seems to interpret the claimed polyclonal IgG are limited to intravenous immune globulin derived from pools of human plasma that are suitable for intravenous administration as

described in Tankersley, Lemm and Cramer references but antibody art recognizes the polyclonal IgG to include any antibody that binds to multiple epitopes.

Further, Appellant has asserted that the polyclonal IgG preparations have unique stability challenges that are associated with purification procedures of ethanol precipitation and the polyclonal IgG preparations are prone to aggregation, fragmentation and oxidation (p. 16-17 of the Brief).

The stability challenge is not limited to polyclonal IgG as Appellant asserted but it is recognized as a general challenge of the antibody art. The '586 patent discloses that the aggregation, denaturation and size modification (e.g. clipping) are characteristics to determine the stability of physical, chemical and/or biological activities of any antibody (col. 5-6) and these characteristics are linked to determine the stability of the antibody. The '586 patent further teaches addition of sucrose and/or trehalose to add stability to antibody formulation (col. 22, e.g. stabilizer) and the stabilizer is expected to inhibit aggregation, fragmentation and oxidation to improve overall stability of the antibody formulation. Furthermore, the '139 publication teaches a pharmaceutical formulation that comprises a histidine buffer and an amino acid stabilizing agent, proline being the stabilizing agent (see paragraphs 0031 and 0032). Thus, the addition of proline as a stabilizer as taught by the '139 publication ([0032]) would improve the stability of the antibody by inhibiting aggregation, fragmentation and/or oxidation of the antibody. The '139 publication teaches that the CD4-IgG2 shares the sequence identity with the IgG2 constant region (note Fig 1) and uses proline to stabilize the antibody construct, therefore, proline is expected to stabilize the polyclonal antibody or any antibody preparation.

At page 19 of the Brief, Appellant has asserted that the teaching of proline in the '139 publication is irrelevant to solve idiotype-anti-idiotype dimerization observed in the polyclonal IgG.

However, this assertion is irrelevant since the claimed invention as instantly pending does not recite the limitation of stability. The asserted remedy for idiotype-anti-idiotype dimerization is not required in the claimed invention.

The specification of the instant application does not specifically define the term "stable". Rather, the specification discloses that the increased stability may mean "better stability of the preparation at temperature between about 2-40°C" (p. 4) and the improved storage time means the invention is stable for at least 30 days (p. 4). Therefore, the preparation is considered stable if the preparation retains its activity at 2°C for 30 days in light of the specification of the instant application. The asserted characteristic is not associated with the definition of being stable and Appellant argues limitations that are not claimed.

Additionally, even though the limitations are not claimed and required, the prior art acknowledges such phenomenon as general stability issues of the antibody. Note that the '586 patent defines the term "stable" and "physical stability" as following:

Preferably, the formulation is stable at room temperature for at least 1 month and/or stable at about 2-8°C for at least 2 years (col. 6, lines 1-3) ... These characteristics include aggregation, precipitation, denaturation and chemical alteration.

Thus, upon achieving stability of the antibody formulation, aggregation, precipitation, denaturation and chemical alteration of the formulation are expected to be improved overall. Given that the motivation to add stabilizer for antibody formulation is taught by the '586 patent and the '139 publication teaches proline acts as an amino acid stabilizer in a pharmaceutical composition comprising CD4-IgG2, it would be obvious to add proline to any antibody formulation to stabilize the formulation.

Therefore, it is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Moreover, Appellant has asserted that neither '586 patent nor the'139 publication suggest a stabilizer comprising a protein at pH within the claimed range (at p. 21-22 of Brief) and

Appellant has further argued that the '586 patent fails to mention proline and it is not obvious to select a proline from various excipients known in the art (p. 22-25 of Brief).

Contrary to Appellant's arguments that the prior art fails to teach the pH of proline at the recited range (p. 21 of Brief), the recited pH (about 4.2 to about 5.4) is not interpreted as the pH of proline, rather the pH of the pharmaceutical composition. As it is recited in claim 40, "wherein the preparation has a pH of about 4.2 to about 5.4" or as in claim 29, ", wherein the preparation comprises polyclonal IgG and a stabilizer comprising proline, has a pH of about 4.2 to about 5.4". Further, the specification does not disclose any particular mention of the specific pH of proline as Appellant has argued. Thus, the recited pH of about 4.2 to about 5.4 is proper to be interpreted as the pH of the formulation and both the '586 patent and the '139 publication provide such teaching as Appellant has acknowledged (p. 22 of the Brief). Given that the term "about" is considered flexible and broad, the term about includes pH near pH 4.8 and pH 5.4. Regardless, the claimed pH 5.4 is included in the prior art pH ranges.

With respect to Appellant's arguments that there is no motivation to select the proline as a stabilizer among various excipients and stabilizers known in the art, it is noted that the '139 publication provides a finite number of amino acid stabilizers (alanine, glycine, proline and glycylglycine). Therefore, one of skill in the art would immediately envisage amino acid substitutions or addition among the finite list of the amino acids from the '139 publication and one of skill in the art would choose from this finite number of identified residues with a reasonable expectation of success absent any objective evidence of unexpected results.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according to known methods to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (antibody and proline) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (stabilization of protein) with no change in their respective functions and the combination would have yielded nothing more than predictable results of yielding more stable composition.

B) Use of known technique to improve similar products in the same way.

The rationale to support a conclusion that the claims would have been obvious is that a method of stabilizing antibody formulation is taught by the '586 patent was made part of ordinary capabilities of one skilled in the art based upon the teachings of the '139 publication. One of ordinary skill in the art would have been capable of applying the known methods of adding amino acid stabilizer to add stability of the antibody and the results would have been predictable to one of ordinary skill in the art.

C) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. amino acid stabilizers taught by the '139 publication) within his or her technical grasp. This leads to the anticipated success of stabilizing effect of antibody or the construct having IgG, it is likely the product not of innovation but of ordinary skill and common sense.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."

Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

As discussed, as used in the '586 patent, the polyclonal antibody is encompassed by the term "antibody" (note col. 7) and the '139 publication teaches the use of proline an amino acid stabilizer in an antibody preparation.

Moreover, Appellant has asserted that the claimed invention showed unexpected results and commercial success (p. 24-28 of the Brief). Appellant has provided information about HIZENTRA® and PRIVIGEN® to support this assertion.

The product information sheets of HIZENTRA® and PRIVIGEN® reveal that the HIZENTRA® consisting of human IgG and 250mM of proline and Tween and the pH of the formulation is at 4.6 -5.2 (see p.156 of the reference) and PRIVIGEN® consisting of human IgG and 250 mM of proline and the pH of the formulation is at pH 4.8 (p. 13 of the reference), respectively.

Appellant has further asserted that maintenance or extension of shelf-life or stability of the liquid preparation for 2-3 years are unexpected. Cramer reference is submitted to substantiate this assertion.

However, the secondary consideration is not sufficient to obviate the evidence of obviousness and the scope of the claimed invention is not commensurate with the references submitted by Applicant.

Note that the excerpt discloses that the formulation consisting of proline and antibody can be stored at room temperature for 2-3 years while the claimed formulation comprising a proline and antibody. The term comprising is considered open and it allows addition of other unrecited stabilizers and amino acids in addition to proline. Note that the '586 patent teaches addition of polysorabate (e.g. Tween) in the antibody formulation and being stable for at least 2 years at 2-8°C (see claims 1, 15, 20-21). Given that the antibody formulation comprising antibody, buffer and Tween is stable for at least for 2 years (note no upper limit is recited) and the addition of proline which is known to stabilize IgG construct would expected to extend the shelf life. Note that the independent claim 29 does not need to be in the aqueous form and/or as in the room temperature for 2-3 years as applicant has asserted. Such conditions of the preparation or the property which Appellant relies on to show the unexpected results are not claimed. Appellant argues the limitations that are not recited in the claims.

With respect to Cramer reference teaching the liquid intravenous immune globulin (IVIG), as discussed above, the claimed polyclonal IgG is not limited to human immune globulins prepared from pools of human plasma by ethanol precipitation or the preparation is not limited to polyclonal IgG and proline and Tween (for HIZENTRA®) or liquid intravenous immune globulin (IVIG). Thus, the secondary consideration argued by the appellants is not sufficient to obviate the obviousness and the scope of the claimed invention is not commensurate with the references submitted by Appellant.

It is noted that Appellant has not addressed any commercial success, rather, unexpected results of showing maximum of 36 months at room temperature are discussed (at p. 27-28, of the Brief).

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As discussed above, the prior art teaches polyclonal IgG and motivation to use proline as a stabilizer and the asserted unexpected results relying on the characteristics or conditions that are not claimed is not sufficient to obviate the rejection of record.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skilled in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

(11) Related Proceeding(s) Appendix

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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December 8, 2011

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